

Citalopram May Ease Depression in Heart Disease

BY JANE SALODOF MACNEIL
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TUCSON, ARIZ. — A randomized, multicenter Canadian trial testing interpersonal psychotherapy and citalopram in 284 depressed patients with stable coronary artery disease produced mixed results, investigators reported at the annual meeting of the Academy of Psychosomatic Medicine.

Citalopram (Celexa) was significantly

more effective than placebo, reducing Hamilton Depression Rating scale (HAM-D) scores by an additional 3.3 points on average, according to Dr. François Lespérance, principal investigator of the Canadian Cardiac Randomized Evaluation of Antidepressant and Psychotherapy Efficacy (CREATE) trial.

Adding interpersonal psychotherapy (IPT) to 12 weekly clinical management sessions was a disappointment, however. Short-term therapy turned out to be no

more effective in relieving depression than clinical management alone.

The Canadian Institutes of Health Research gave the CREATE trial a \$1,342,996 (Canadian) grant. Starting in 2002, the study enrolled patients in Montreal, Kingston, Ottawa, and Toronto. Faced with slow enrollment, it added sites in Halifax and Calgary.

To maximize resources, the investigators randomized patients twice under a 2-by-2 factorial trial design. The participants comprised four cohorts: IPT/clinical man-

agement and citalopram (67 patients), IPT/clinical management and placebo (75 patients), clinical management alone and citalopram (75 patients), and clinical management alone and placebo (67 patients).

Consequently, the analyses were based on 142 patients exposed to IPT/clinical management vs. 142 patients exposed to clinical management alone and 142 patients treated with citalopram vs. 142 treated with placebo.

The presentation did not address the combined effect of IPT and citalopram in patients given both therapies.

Dr. Nancy Frasure-Smith, a coinvestigator, said the investigators neither expected nor saw any synergy between IPT and citalopram.

Dr. Frasure-Smith, a professor of psychiatry at McGill University in Montreal and senior research associate at the Montreal Heart Institute, emphasized that the trial used broad inclusion criteria. She cited growing evidence that depression is a



Brief Summary of Prescribing Information
05-1114

ROZEREM™

(ramelteon) Tablets

INDICATIONS AND USAGE

ROZEREM is indicated for the treatment of insomnia characterized by difficulty with sleep onset.

CONTRAINDICATIONS

ROZEREM is contraindicated in patients with a hypersensitivity to ramelteon or any components of the ROZEREM formulation.

WARNINGS

Since sleep disturbances may be the presenting manifestation of a physical and/or psychiatric disorder, symptomatic treatment of insomnia should be initiated only after a careful evaluation of the patient. The failure of insomnia to remit after a reasonable period of treatment may indicate the presence of a primary psychiatric and/or medical illness that should be evaluated. Worsening of insomnia, or the emergence of new cognitive or behavioral abnormalities, may be the result of an unrecognized underlying psychiatric or physical disorder and requires further evaluation of the patient. As with other hypnotics, exacerbation of insomnia and emergence of cognitive and behavioral abnormalities were seen with ROZEREM during the clinical development program.

ROZEREM should not be used by patients with severe hepatic impairment.

ROZEREM should not be used in combination with fluvoxamine (see PRECAUTIONS: Drug Interactions).

A variety of cognitive and behavior changes have been reported to occur in association with the use of hypnotics. In primarily depressed patients, worsening of depression, including suicidal ideation, has been reported in association with the use of hypnotics.

Patients should avoid engaging in hazardous activities that require concentration (such as operating a motor vehicle or heavy machinery) after taking ROZEREM.

After taking ROZEREM, patients should confine their activities to those necessary to prepare for bed.

PRECAUTIONS

General

ROZEREM has not been studied in subjects with severe sleep apnea or severe COPD and is not recommended for use in those populations.

Patients should be advised to exercise caution if they consume alcohol in combination with ROZEREM.

Use in Adolescents and Children

ROZEREM has been associated with an effect on reproductive hormones in adults, e.g. decreased testosterone levels and increased prolactin levels. It is not known what effect chronic or even chronic intermittent use of ROZEREM may have on the reproductive axis in developing humans (see Pediatric Use).

Information for Patients

Patients should be advised to take ROZEREM within 30 minutes prior to going to bed and should confine their activities to those necessary to prepare for bed.

Patients should be advised to avoid engaging in hazardous activities (such as operating a motor vehicle or heavy machinery) after taking ROZEREM.

Patients should be advised that they should not take ROZEREM with or immediately after a high fat meal.

Patients should be advised to consult their health care provider if they experience worsening of insomnia or any new behavioral signs or symptoms of concern.

Patients should consult their health care provider if they experience one of the following: cessation of menses or galactorrhea in females, decreased libido, or problems with fertility.

Laboratory Tests

No standard monitoring is required.

For patients presenting with unexplained amenorrhea, galactorrhea, decreased libido, or problems with fertility, assessment of prolactin levels and testosterone levels should be considered as appropriate.

Drug Interactions

ROZEREM has a highly variable inter-subject pharmacokinetic profile (approximately 100% coefficient of variation in C_{max} and AUC). As noted above, CYP1A2 is the major isozyme involved in the metabolism of ROZEREM; the CYP2C2 subfamily and CYP3A4 isozymes are also involved to a minor degree.

Effects of Other Drugs on ROZEREM Metabolism

Fluvoxamine (strong CYP1A2 inhibitor): When fluvoxamine 100 mg twice daily was administered for 3 days prior to single-dose co-administration of ROZEREM 16 mg and fluvoxamine, the AUC_{0-12} for ramelteon increased approximately 190-fold, and the C_{max} increased approximately 70-fold, compared to ROZEREM administered alone. ROZEREM should not be used in combination with fluvoxamine (see WARNINGS). Other less potent CYP1A2 inhibitors have not been adequately studied. ROZEREM should be administered with caution to patients taking less strong CYP1A2 inhibitors.

Rifampin (strong CYP enzyme inducer): Administration of rifampin 600 mg once daily for 11 days resulted in a mean decrease of approximately 80% (40% to 90%) in total exposure to ramelteon and metabolite M-II, (both AUC_{0-12} and C_{max}) after a single 32 mg dose of ROZEREM. Efficacy may be reduced when ROZEREM is used in combination with strong CYP enzyme inducers such as rifampin.

Ketoconazole (strong CYP3A4 inhibitor): The AUC_{0-12} and C_{max} of ramelteon increased by approximately 84% and 36%, respectively, when a single 16 mg dose of ROZEREM was administered on the fourth day of ketoconazole 200 mg twice daily administration, compared to administration of ROZEREM alone. Similar increases were seen in M-II pharmacokinetic variables. ROZEREM should be administered with caution in subjects taking strong CYP3A4 inhibitors such as ketoconazole.

Fluconazole (strong CYP2C9 inhibitor): The total and peak systemic exposure (AUC_{0-12} and C_{max}) of ramelteon after a single 16 mg dose of ROZEREM was increased by approximately 150% when administered with fluconazole. Similar increases were also seen in M-II exposure. ROZEREM should be administered with caution in subjects taking strong CYP2C9 inhibitors such as fluconazole.

Interaction studies of concomitant administration of ROZEREM with fluoxetine (CYP2D6 inhibitor), omeprazole (CYP1A2 inducer/CYP2C19 inhibitor), theophylline (CYP1A2 substrate), and dextromethorphan (CYP2D6 substrate) did not produce clinically meaningful changes in either peak or total exposures to ramelteon or the M-II metabolite.

Effects of ROZEREM on Metabolism of Other Drugs

Concomitant administration of ROZEREM with omeprazole (CYP2C19 substrate), dextromethorphan (CYP2D6 substrate), midazolam (CYP3A4 substrate), theophylline (CYP1A2 substrate), digoxin (p-glycoprotein substrate), and warfarin (CYP2C9 [S]/CYP1A2 [R] substrate) did not produce clinically meaningful changes in peak and total exposures to these drugs.

Effect of Alcohol on Rozerem

Alcohol: With single-dose, daytime co-administration of ROZEREM 32 mg and alcohol (0.6 g/kg), there was no clinically meaningful or statistically sig-

nificant effects on peak or total exposure to ROZEREM. However, an additive effect was seen on some measures of psychomotor performance (i.e., the Digit Symbol Substitution Test, the Psychomotor Vigilance Task Test, and a Visual Analog Scale of sedation) at some post-dose time points. No additive effect was seen on the Delayed Word Recognition Test. Because alcohol by itself impairs performance, and the intended effect of ROZEREM is to promote sleep, patients should be cautioned not to consume alcohol when using ROZEREM.

Drug/Laboratory Test Interactions

ROZEREM is known to interfere with commonly used clinical laboratory tests. In addition, *in vitro* data indicate that ramelteon does not cause false-positive results for benzodiazepines, opiates, barbiturates, cocaine, cannabinoids, or amphetamines in two standard urine drug screening methods *in vitro*.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis
In a two-year carcinogenicity study, B6C3F₁ mice were administered ramelteon at doses of 0, 30, 100, 300, or 1000 mg/kg/day by oral gavage. Male mice exhibited a dose-related increase in the incidence of hepatic tumors at dose levels ≥ 100 mg/kg/day including hepatic adenoma, hepatic carcinoma, and hepatoblastoma. Female mice developed a dose-related increase in the incidence of hepatic adenomas at dose levels ≥ 300 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors in male mice was 30 mg/kg/day (103-times and 3-times the therapeutic exposure to ramelteon and the active metabolite M-II, respectively, at the maximum recommended human dose [MRHD] based on an area-under-the-curve [AUC] comparison). The no-effect level for hepatic tumors in female mice was 100 mg/kg/day (827-times and 12-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

In a two-year carcinogenicity study conducted in the Sprague-Dawley rat, male and female rats were administered ramelteon at doses of 0, 15, 50, 250 or 1000 mg/kg/day by oral gavage. Male rats exhibited a dose-related increase in the incidence of hepatic adenoma and benign Leydig cell tumors of the testes at dose levels ≥ 250 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. Female rats exhibited a dose-related increase in the incidence of hepatic adenoma at dose levels ≥ 60 mg/kg/day and hepatic carcinoma at the 1000 mg/kg/day dose level. The no-effect level for hepatic tumors and benign Leydig cell tumors in male rats was 60 mg/kg/day (1.429-times and 12-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC). The no-effect level for hepatic tumors in female rats was 15 mg/kg/day (472-times and 16-times the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

The development of hepatic tumors in rodents following chronic treatment with non-genotoxic compounds may be secondary to microsomal enzyme induction, a mechanism for tumor generation not thought to occur in humans. Leydig cell tumor development following treatment with non-genotoxic compounds in rodents has been linked to reductions in circulating testosterone levels with compensatory increases in luteinizing hormone release, which is a known proliferative stimulus to Leydig cells in the rat testis. Rat Leydig cells are more sensitive to the stimulatory effects of luteinizing hormone than human Leydig cells. In mechanistic studies conducted in the rat, daily ramelteon administration at 250 and 1000 mg/kg/day for 4 weeks was associated with a reduction in plasma testosterone levels. In the same study, luteinizing hormone levels were elevated over a 24 hour period after the last ramelteon treatment; however, the durability of this luteinizing hormone finding and its support for the proposed mechanistic explanation was not clearly established.

Although the rodent tumors observed following ramelteon treatment occurred at plasma levels of ramelteon and M-II in excess of mean clinical plasma concentrations at the MRHD, the relevance of both rodent hepatic tumors and benign rat Leydig cell tumors to humans is not known.

Mutagenesis

Ramelteon was not genotoxic in the following: *in vitro* bacterial reverse mutation (Ames) assay; *in vitro* mammalian cell gene mutation assay using the mouse lymphoma TK⁺ cell line; *in vivo/in vitro* unscheduled DNA synthesis assay in rat hepatocytes; and *in vivo* micronucleus assays conducted in mouse and rat. Ramelteon was positive in the chromosomal aberration assay in Chinese hamster lung cells in the presence of S9 metabolic activation. Separate studies indicated that the concentration of the M-II metabolite formed by the rat liver S9 fraction used in the *in vitro* genetic toxicology studies described above, exceeded the concentration of ramelteon; therefore, the genotoxic potential of the M-II metabolite was also assessed in these studies.

Impairment of Fertility

Ramelteon was administered to male and female Sprague-Dawley rats in an initial fertility and early embryonic development study at dose levels of 6, 60, or 600 mg/kg/day. No effects on male or female mating or fertility were observed with a ramelteon dose up to 600 mg/kg/day (786-times higher than the MRHD on a mg/m² basis). Irregular estrus cycles, reduction in the number of implants, and reduction in the number of live embryos were noted with dosing females at ≥ 60 mg/kg/day (79-times higher than the MRHD on a mg/m² basis). A reduction in the number of corpora lutea occurred at the 600 mg/kg/day dose level. Administration of ramelteon up to 600 mg/kg/day to male rats for 7 weeks had no effect on sperm quality and when the treated male rats were mated with untreated female rats there was no effect on implants or embryos. In a repeat of this study using oral administration of ramelteon at 20, 60 or 200 mg/kg/day for the same study duration, females demonstrated irregular estrus cycles with dosing ≥ 60 mg/kg/day, but no effects were seen on implantation or embryo viability. The no-effect dose for fertility endpoints was 20 mg/kg/day in females (26-times the MRHD on a mg/m² basis) and 600 mg/kg/day in males (786-times higher than the MRHD on a mg/m² basis) when considering all studies.

Pregnancy: Pregnancy Category C

Ramelteon has been shown to be a developmental teratogen in the rat when given in doses 197 times higher than the maximum recommended human dose [MRHD] on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women. Ramelteon should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The effects of ramelteon on embryo-fetal development were assessed in both the rat and rabbit. Pregnant rats were administered ramelteon by oral gavage at doses of 0, 10, 40, 150, or 600 mg/kg/day during gestation days 6-17, which is the period of organogenesis in this species. Evidence of maternal toxicity and fetal teratogenicity was observed at doses greater than or equal to 150 mg/kg/day. Maternal toxicity was chiefly characterized by decreased body weight and, at 600 mg/kg/day, ataxia and decreased spontaneous movement. At maternally toxic doses (150 mg/kg/day or greater), the fetuses demonstrated visceral malformations consisting of diaphragmatic hernia and minor anatomical variations of the skeleton (irregularly shaped scapula). At 600 mg/kg/day, reductions in fetal body weights and malformations including cysts on the external genitalia were additionally observed. The no-effect level for teratogenicity in this study was 40 mg/kg/day (1,892-times and 45-times higher than the therapeutic exposure to ramelteon and the active metabolite M-II, respectively, at the MRHD based on an area-under-the-curve [AUC] comparison). Pregnant rabbits were administered ramelteon by oral gavage at doses of 0, 12, 60, or 300 mg/kg/day during gestation days 6-18, which is the period of organogenesis in this species. Although maternal toxicity was apparent with a ramelteon dose of 300 mg/kg/day, no evidence of fetal effects or teratogenicity was associated with any dose level. The no-effect level for teratogenicity was, therefore, 300 mg/kg/day (11,862-times and 99-times

higher than the therapeutic exposure to ramelteon and M-II, respectively, at the MRHD based on AUC).

The effects of ramelteon on pre- and post-natal development in the rat were studied by administration of ramelteon to the pregnant rat by oral gavage at doses of 0, 30, 100, or 300 mg/kg/day from day 6 of gestation through parturition to postnatal (lactation) day 21, at which time offspring were weaned. Maternal toxicity was noted at doses of 100 mg/kg/day or greater and consisted of reduced body weight gain and increased adrenal gland weight. Reduced body weight during the post-weaning period was also noticed in the offspring of the groups given 100 mg/kg/day and higher. Offspring in the 300 mg/kg/day group demonstrated physical and developmental delays including delayed eruption of the lower incisors, a delayed acquisition of the righting reflex, and an alteration of emotional response. These delays are often observed in the presence of reduced offspring body weight but may still be indicative of developmental delay. An apparent decrease in the viability of offspring in the 300 mg/kg/day group was likely due to altered maternal behavior and function observed at this dose level. Offspring of the 300 mg/kg/day group also showed evidence of diaphragmatic hernia, a finding observed in the embryo-fetal development study previously described. There were no effects on the reproductive capacity of offspring and the resulting progeny were not different from those of vehicle-treated offspring. The no-effect level for pre- and postnatal development in this study was 30 mg/kg/day (39-times higher than the MRHD on a mg/m² basis).

Labor and Delivery

The potential effects of ROZEREM on the duration of labor and/or delivery, for either the mother or the fetus, have not been studied. ROZEREM has no established use in labor and delivery.

Nursing Mothers

Ramelteon is secreted into the milk of lactating rats. It is not known whether this drug is excreted in human milk. No clinical studies in nursing mothers have been performed. The use of ROZEREM in nursing mothers is not recommended.

Pediatric Use

Safety and effectiveness of ROZEREM in pediatric patients have not been established. Further study is needed prior to determining that this product may be used safely in pre-pubescent and pubescent patients.

Geriatric Use

A total of 654 subjects in double-blind, placebo-controlled, efficacy trials who received ROZEREM were at least 65 years of age; of these, 199 were 75 years of age or older. No overall differences in safety or efficacy were observed between elderly and younger adult subjects.

ADVERSE REACTIONS

Overview

The data described in this section reflect exposure to ROZEREM in 4251 subjects, including 346 exposed for 6 months or longer, and 473 subjects for one year.

Adverse Reactions Resulting in Discontinuation of Treatment

Five percent of the 3594 individual subjects exposed to ROZEREM in clinical studies discontinued treatment owing to an adverse event, compared with 2% of the 1370 subjects receiving placebo. The most frequent adverse events leading to discontinuation in subjects receiving ROZEREM were somnolence (0.8%), dizziness (0.5%), nausea (0.3%), fatigue (0.3%), headache (0.3%), and insomnia (0.3%).

ROZEREM Most Commonly Observed Adverse Events in Phase 1-3 trials

The incidence of adverse events during the Phase 1 through 3 trials (% placebo, n=1370; % ramelteon [8 mg], n=1250) were: headache NOS (7%, 7%), somnolence (3%, 5%), fatigue (2%, 4%), dizziness (3%, 5%), nausea (2%, 3%), insomnia exacerbated (2%, 3%), upper respiratory tract infection NOS (2%, 3%), diarrhea NOS (2%, 2%), myalgia (1%, 2%), depression (1%, 2%), dyspnea (1%, 2%), arthralgia (1%, 2%), influenza (0, 1%), blood cortisol decreased (0, 1%).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of other drugs, and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

DRUG ABUSE AND DEPENDENCE

ROZEREM is not a controlled substance.

Human Data: See the CLINICAL TRIALS section, Studies Pertinent to Safety Concerns for Sleep-Promoting Agents in the Complete Prescribing Information.

Animal Data. Ramelteon did not produce any signals from animal behavioral studies indicating that the drug produces rewarding effects. Monkeys did not self-administer ramelteon and the drug did not induce a conditioned place preference in rats. There was no generalization between ramelteon and midazolam. Ramelteon did not affect rotarod performance, an indicator of disruption of motor function, and it did not potentiate the ability of diazepam to interfere with rotarod performance. Discontinuation of ramelteon in animals or in humans after chronic administration did not produce withdrawal signs. Ramelteon does not appear to produce physical dependence.

OVERDOSAGE

Signs and Symptoms

No cases of ROZEREM overdose have been reported during clinical development. ROZEREM was administered in single doses up to 160 mg in an abuse liability trial. No safety or tolerability concerns were seen.

ROZEREM was administered in single doses up to 160 mg in an abuse liability trial. No safety or tolerability concerns were seen. Hemodialysis does not effectively reduce exposure to ROZEREM. Therefore, the use of dialysis in the treatment of overdose is not appropriate.

Poison Control Center

As with the management of all overdoses, the possibility of multiple drug ingestion should be considered. The physician may contact a poison control center for current information on the management of overdose.

Rx only

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540-8645 Osaka, JAPAN

Manufactured in:

Takeda Pharmaceutical Company, Ltd.
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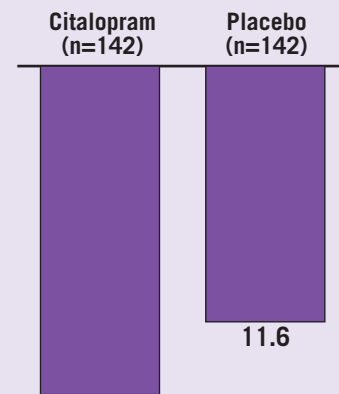
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References: 1. Rozerem package insert, Takeda Pharmaceuticals America, Inc. 2. Johnson MW, Suss PE, Griffiths RR. Ramelteon: a novel hypnotic lacking abuse liability and sedative side effects. *Arch Gen Psychiatry.* In press.

Point Reduction in HAM-D Scores



Source: Dr. Lespérance

risk factor for heart disease, but said little is known about treating depression in coronary disease patients because most depression treatment trials exclude patients with comorbidities.

In addition to having stable coronary artery disease, patients entered the CREATE trial having a current major depressive episode lasting at least 4 weeks based on the Structured Clinical Interview for Depression (SCID) and a baseline score of 19 or more on the 24-item Hamilton Depression Rating scale (HAM-D).

In the medication arms described by Dr. Lespérance, chief of psychiatry at the Centre Hospitalier de l'Université de Montréal, citalopram or placebo was titrated up from 10 mg per day during the first week to 20 mg per day for the next 5 weeks. If a patient's HAM-D score did not fall to 8 or less by week 6, the dose was increased to 40 mg per day for the duration of the study. Dr. Lespérance said the average dose was 33 mg per day by the end of the trial.

The advantage of citalopram over placebo was evident by the sixth week, he said. By the end of the trial, HAM-D scores fell by 14.9 points with citalopram and 11.6 points with placebo. Similar effects were

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reported on the Beck Depression Inventory and the Inventory for Depressive Symptomatology.

Although side effects typical of selective serotonin reuptake inhibitors (SSRIs) were reported, Dr. Lespérance said cardiovascular side effects were rare and small with no difference between groups. CREATE gave “no evidence that we

Does Treatment Reduce Deaths?

CREATE was the third large clinical trial to investigate treatment of major depressive disorder in heart disease patients.

In the Sertraline Antidepressant Heart Attack Randomized Trial (SAD-HART), investigators did not find the selective serotonin reuptake inhibitor sertraline (Zoloft) to be significantly better than placebo in reducing depressive symptoms for the population overall, but it was safe and more effective for recurrent depression in patients with a recent myocardial infarction or unstable angina (JAMA 2002;288:701-9).

In the Enhancing Recovery in Coronary Heart Disease (ENRICH) trial, investigators compared 6 months of cognitive-behavioral therapy supplemented as needed with sertraline with usual care in 2,481 patients who were depressed when enrolled 1 month after an acute myocardial infarction. Changes on the Hamilton Depression Scale were statistically significant, but therapy had no impact on the primary outcomes of the study: death or recurrent myocardial infarction (JAMA 2003;289:3106-16).

The direct effect that lowering cholesterol or relieving depression has on heart disease may never be known, said Dr. Nancy Frasure-Smith, a CREATE investigator, in a plenary lecture before release of the CREATE results at the Academy of Psychosomatic Medicine meeting. Statins and antidepressants have pleiotropic effects, she said; they can affect multiple systems or metabolic processes. With respect to antidepressants, she cited human and animal studies showing impacts on platelet activation, endothelial function, C-reactive protein levels, and inflammation.

“If any of these treatments improves prognosis in coronary artery disease patients, we’ll know [it] should be widely used because it helps improve survival,” she said. “But because of the pleiotropic effects of most available depressant treatments, we will not know what the impact is because of a change in depression itself.” Depression should be treated in its own right, she advised, reminding cardiologists about “the compliance issue:” Depressed patients are less likely to adhere to treatment of their coronary artery disease.

should be concerned about cardiac safety,” he said. As for evidence that SSRIs might be cardioprotective, he cautioned that the data are inconclusive.

The investigators conducted a biomarker analysis that found treatment with citalopram was associated with enhanced production of nitric oxide. Dr. Louis T. van Zyl, a coinvestigator from Queens University in Kingston (Ont.), said the clinical implications are unclear. He added, however, that increasing nitric oxide might reduce cardiovascular risk.

All of the patients received 15-20 minutes of clinical management each week. During these sessions, therapists re-

viewed patient progress and side effects, according to Dr. J. Robert Swenson, a coinvestigator from the University of Ottawa Heart Institute.

Weekly IPT sessions were limited to 45 minutes duration and 12 weeks in all, he said. Patients assigned to IPT had to choose one issue to focus upon in short-term therapy, which typically followed clinical management.

Dr. Swenson said patients who received clinical management without IPT did slightly better halfway through the trial. No significant difference was found at 12 weeks, as he reported about half the patients in both groups responded to treat-

ment, and a third went into remission.

Therapists who were experienced in IPT or specially trained for the trial delivered both the clinical management and IPT sessions.

This use of the IPT therapists for clinical management generated extensive discussion at the meeting. Despite assurances by the investigators that the clinical management sessions were closely monitored, some audience members questioned whether the clinical management-alone arm received more therapy than a nurse practitioner would deliver as usual care to similar patients who were outside of the trial. ■

Are her symptoms more *typical* than *atypical*?

Although chest pain is the most common symptom of myocardial infarction among both sexes,¹ women often present with symptoms that are not typically seen in men.² Coronary heart disease can be different in women, and many challenges exist in risk stratification and decision making.^{3,4}

Myocardial perfusion imaging (MPI) can provide important risk stratification information in women.⁴ Approximately 40% of women referred for MPI are candidates for pharmacologic stress.³ For those unable to exercise adequately, Adenoscan stress provides interpretable MPI results in 98.7% of patients.⁵

COMMITTED TO HER HEART®

IMPORTANT SAFETY INFORMATION

Intravenous Adenoscan® (adenosine injection) is indicated as an adjunct to thallium-201 myocardial perfusion scintigraphy in patients unable to exercise adequately.

Approximately 2.6% and 0.8% of patients developed second- and third-degree AV block, respectively. All episodes of AV block have been asymptomatic, transient, and did not require intervention; less than 1% required termination of adenosine infusion.

Fatal cardiac arrest, sustained ventricular tachycardia (requiring resuscitation), and non-fatal myocardial infarction have been reported coincident with Adenoscan infusion. Patients with unstable angina may be at greater risk.

Side effects that were seen most often included flushing (44%), chest discomfort (40%), and dyspnea (28%). Side effects usually resolve quickly when infusion is terminated and generally do not interfere with test results.

Despite adenosine's short half-life, 10.6% of the side effects started several hours after the infusion terminated, and 8.4% of the side effects that began during the infusion persisted for up to 24 hours after infusion. In many cases, it is not possible to know whether these late adverse events are the result of Adenoscan infusion.

Please see brief summary of prescribing information on the next page.

1. Isaac D, et al. *Can J Cardiol*. 2001;17(suppl D):38D-48D. 2. Wenger NK. *Cardiovasc Res*. 2002;53:558-567. 3. Mieres JH, et al. *J Nucl Cardiol*. 2003;10:95-101. 4. Hachamovitch R, et al. *J Am Coll Cardiol*. 1996;28:34-44. 5. Cerqueira MD, et al. *J Am Coll Cardiol*. 1994;23:384-389.

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